in EMBASE and MEDLINE, search terms ‚hemophilia B' and ‚FIX'. Inclusion criteria: journal articles (JA), conference abstracts (CA), English language, published between January 2009 and March 2013, studies only. Screening of titles, abstracts and full texts was performed subsequently. Registered trials (RT) concerning HB or FIX were identified in ClinicalTrials.gov. Analysis comprised age group, sponsor, research topic, recruitment status, and study design. **RESULTS:** Screening of 1,639 hits yielded 31 JA describing 35 studies, and 62 CA. FIX was the topic of 21 studies (60.0%) and 29 CA (46.8%). A total of 7 studies focused on various aspects of HB, 6 on haemophilia studies with separate data on HB. Gene therapy was the main focus of 2 JA and 11 CA (17.7%). Screening of 173 hits from ClinicalTrials.gov yielded 47 RT, 42 unpublished. Overall 32 unpublished RT (76.2%) concerned FIX, and 4 (9.5%) gene therapy. Randomized study design was described in one study (2.9%) and 4 RT (9.5%), and 3 studies (8.6%) and 7 RT (16.7%) were prospective observational comparative. **CONCLUSIONS:** Randomized study design or comparator arms were uncommon, and payers' requirements for evidence were not met. Therefore, randomization, comparison to standard of care and documentation of outcome should be discussed. Development of refined statistical methods and exploitation of complementary data like real-life data may help to fill actual evidence gaps in rare diseases.

PRM213
THE ROLE OF DSM IN THE EMA AND FDA AUTHORIZATION PROCESS FOR PSYCHIATRIC DRUGS
Meyers OI
Truven Health Analytics, Cleveland, OH, USA
OBJECTIVES: In May 2013, the American Psychiatric Association released the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This is significant for clinicians, researchers, and developers of psychopharmacologic drugs. The previous version of the DSM, the DSM-IV-TR, was published in 2000 and the last time the diagnostic criteria were revised was in 1994, when the DSM-IV was published. The objective of this review was to determine how much of a role DSM has played in the drug approval process in Europe and the US. **METHODS:** For drugs authorized since 2000, summaries of product characteristics (SPCs; EMA) and approved labels (FDA) were reviewed to determine how frequently the DSM is mentioned in the "clinical particulars" or "indications" sections and how frequently DSM criteria are mentioned in the clinical trials sections of the SPCs or labels. The review focused on schizophrenia and psychotic disorders, mood disorders, and for the FDA, attention-deficit/hyperactivity disorder as well. **RESULTS:** For EMA-authorized products, 8 EPARs met the criteria with 10 indications in total. The DSM was never mentioned in the indications or posology sections, but in 7 (70%) of the descriptions of pharmacodynamic properties (section 5.1), DSM criteria were cited as the study inclusion criteria. For FDA-approved products, 17 labels with 22 indications met the review criteria. The DSM was mentioned in 10 of the indications sections (45%) and DSM criteria were cited as inclusion criteria in 20 instances (91%). **CONCLUSIONS:** Regulators in Europe and the US rely heavily on DSM diagnostic criteria, in the sense that these often serve as inclusion criteria for pivotal clinical trials. Given significant changes to the criteria in many diagnostic categories, regulators and sponsors need to familiarize themselves with the document and evaluate their use of DSM criteria going forward.

PRM214
PODCASTS AS A LEARNING TOOL IN A RESEARCH METHODS COURSE FOR PHARMACY STUDENTS
Nguyen TL, Lovett AW, Lundquist LM, Bonner CL
Mercer University College of Pharmacy and Health Sciences, Atlanta, GA, USA
OBJECTIVES: Podcasts (recorded lectures) can be beneficial for all students, particularly English as a second language students who face language barriers when learning in another language. There is limited study on pharmacy student perceptions and podcasts, none from an international perspective. The primary objective was to describe pharmacy students' perceptions on the usefulness of podcasting and a secondary objective was to compare perceptions between native versus non-native English speakers in a pharmacy research course. **METHODS:** All first year pharmacy students (n=157) attending a Research Methods course in 2012 were invited to participate in a survey, which utilized a 4-point Likert Scale (1= strongly disagree, 2=disagree, 3=agree, and 4=strongly agree). Podcasts covered all course topics such as Applied Statistics, Odds Ratio and Relative Risk, Case Reports, Observational Studies, Randomized Controlled Trials, and Economic Evaluations. Descriptive statistics and t-tests were utilized to analyze the data in SPSS. The study was approved by the Institutional Review Board. **RESULTS:** A total of 73% of the class completed the survey (40.2% Caucasian, 32% Asian and 25% African American). A total of 24.1% identified themselves as non-native English speakers, 94.6% lived in the US for greater or equal to 5 years and 66.1% communicated in English at home. The majority of students agreed/strongly agreed that podcasts helped them to prepare for exams (92.9%), podcasts were a useful learning tool (91.2%), promoted understanding of course material (89.3%), helped with missed concepts (96.4%), and facilitated note-taking at their own pace (92.2%) with mean scores 3.34, 3.27, 3.27, 3.48 and 3.48, respectively. Results of the t-test revealed that there is no statistically significant difference between native versus non-native English speaking students in their perceptions of podcast usefulness ($p > .05$). **CONCLUSIONS:** Podcasts are beneficial to a majority of students, despite their language background. Podcasts have the potential to be a valuable learning tool for students taking a research methods course.

PRM215
GRADE FOR QUALITY ASSESSMENT OF EFFICACY AND EFFECTIVENESS STUDIES ON ANTI-TNFS TREATMENT OF RHEUMATOID ARTHRITIS
Taino B, Nobre MRC
INCOR - HCFMUSP, Sao Paulo, Brazil
OBJECTIVES: Assess the quality of evidence on experimental and observational clinical research through the same approach named GRADE (Grading of Recommendations Assessment, Development and Evaluation) **METHODS:** We evaluated the primary endpoint of a random sample from efficacy and effectiveness studies included in a systematic review on the treatment of rheumatoid arthritis with anti-TNFs. The quality assessment was conducted in accordance with the recommendations of the GRADE Working Group available at: www.gradeworkinggroup.org/toolbox/index.htm. It assigns at first high quality for trials and low quality for observational studies. **RESULTS:** The assessment of 8 efficacy and 8 effectiveness studies showed respectively that the quality of evidence were high in 5 and 0; moderate in 3 and 2; low in 0 and 2; and very low in 0 and 4. The risk of bias was present in 3 and 5; imprecision results in 0 and 5; elevated magnitude of effect in 6 and 4; controlled confounding bias in 0 and 3; presence of dose-response gradient in 0 and 1. Indirect evidence and inconsistencies were not found in any of the studies. **CONCLUSIONS:** The quality of evidence of 3 trials and 4 observational studies were downgraded, while 2 observational studies had the quality assessment increased.

PRM216
WHAT VALUE CAN OPERATIONAL FEASIBILITY STUDIES BRING TO POST MARKETING OBSERVATIONAL STUDIES (PMOS)? EXAMPLE OF FEASIBILITY STUDY PERFORMED IN EASTERN EUROPE TO ASSESS HEPATITIS C VIRAL DISEASE/PATIENT MANAGEMENT IN REAL WORLD SETTING
El Kebir S, Bayle D, Gauchoux R
Mapi, Real World Evidence, Lyon, France
OBJECTIVES: Operational feasibility studies provide a good opportunity to assess practicality of large full-scale studies. They are an almost essential pre-requisite and should be well designed with clear objectives. Conducting a pilot study can enhance the likelihood of success of PMOS and potentially help to avoid serious design flaws. The objective of this research is to assess the value of feasibility studies prior to PMOS implementation and highlight the importance of local physicians' feedback. **METHODS:** A feasibility study in 6 Eastern European countries was conducted via collection of physician surveys to assess local standard of care. The feasibility questionnaire was developed to assess operational aspects, such as availability of patient population, site experience and time and willingness to participate. The 37 physicians who received the questionnaire were selected through PubMed; they were all experts who have published regarding HCV infection and were provided with the protocol synopsis **RESULTS:** Out of the 37 selected physicians, 18 gastroenterologists, hepatologists, and infectious disease specialists in Bulgaria, Croatia, The Czech Republic, Hungary, Poland and Romania completed the questionnaire. The participating Physicians were working exclusively in public institutions. The average number of HCV patients seen by year is 140 and out of them 78 are treated by Interferon. They specified that they can enrol 2 eligible patients per month on average. They see their patients frequently during treatment initiation (bi-weekly or monthly). However, the follow-up varies from one country to another (quarterly or semi-annually). Physicians indicated that patient records and data regarding blood tests and procedures are accessible for 100% of the cases. Over 60% of the sites were familiar with Patient Reported Outcomes. Overall, 12 physicians were interested in participating in the Study. **CONCLUSIONS:** The result of this survey helped us documenting routine medical practice and confirming the study design and methodology to be implemented.

PRM217
USE OF SURROGATE OUTCOMES IN HEALTH TECHNOLOGY ASSESSMENTS (HTAS)
Jaksa A, Ho YS, Daniel K
Context Matters, Inc., New York, NY, USA
OBJECTIVES: This study analyzes how frequently surrogate outcomes are used in HTAs and if the validity of these outcomes are discussed and reported within the HTAs. A surrogate outcome is defined by the National Institutes of Health as a biomarker intended to substitute for a clinical endpoint. A surrogate outcome is used when a clinical endpoint of interest is not ideal or does not occur often enough to perform meaningful statistical analysis. It is appropriate to use a surrogate outcome only when there is a strong correlation with the clinical endpoint. Before using surrogate outcomes researchers should confirm that the surrogate outcome is biologically plausible, has a magnitude of association with the clinical endpoint, and reflects changes in the relevant clinical endpoint. **METHODS:** Context Matters (CM) analyzed 1,056 HTAs spanning 38 disease conditions. Each HTA had a primary outcome that could be classified as either a surrogate outcome or a clinical endpoint. Data was analyzed for eight HTA agencies: AHRQ, DERP, SMC, HAS, PBAC, NICE, CADTH, and HIS Scotland. For those HTAs using a surrogate outcome as the primary outcome, CM then determined if the HTA agency reported the use of the surrogate and/or discussed the surrogate outcome's validity. **RESULTS:** Ninety-one percent of HTAs used a surrogate outcome (966 HTAs), but only 11% (109 HTAs) identified it as a surrogate outcome and/or discussed its validity. The agencies that discussed the use of the surrogate outcome most often were AHRQ, DERP, and HIS Scotland at 48.1%, 28.6%, and 29.0% of the time, respectively. **CONCLUSIONS:** Surrogate endpoints are prevalent in HTAs, but the agencies rarely discuss the validity of these endpoints. All agencies failed to discuss the use of the surrogate endpoint in over 50% of their reviews. HTA agencies are not following best practice use of surrogate outcomes.

RESEARCH ON METHODS – Conceptual Papers

PRM218
PROPOSAL OF ECONOMIC EVALUATION GUIDELINE IN JAPAN
Fukuda T[1], Akazawa M[2], Fukuda H[3], Igarashi A[4], Ikeda S[5], Ishida H[6], Kobayashi M[7], Moriwaki K[8], Noto S[8], Sakamaki H[9], Saito S[10], Shimozuma K[11], Shiroiwa T[1], Takura T[12], Tomita N[13]
[1]*National Institute of Public Health, Saitama, Japan,* [2]*Meiji Pharmaceutical University, Tokyo, Japan,* [3]*Institute for Health Economics and Policy, Tokyo, Japan,* [4]*Tokyo Univ. Faculty of Pharmacy, Tokyo, Japan,* [5]*International University of Health and Welfare, Otawara City, Tochigi, Japan,*

[6]Yamaguchi University Hospital, Ube, Yamaguchi, Japan, [7]CRECON Research & Consulting Inc, Tokyo, Japan, [8]Niigata University of Health and Welfare, Niigata, Japan, [9]Meijo University, Nagoya, Japan, [10]Okayama University, Okayama, Japan, [11]Ritsumeikan University, Kusatsu, Japan, [12]Osaka University, Osaka, Japan, [13]National Institute of Public Health, Wako, Japan

OBJECTIVES: Use of economic evaluation of health care technologies is intensively discussed in the government in Japan. In order to make evaluation results comparable, standardized method of evaluation is required. We proposed an economic evaluation guideline in Japan. **METHODS:** We organized a research team for developing guideline. After reviewing guidelines in HTA agencies in the world and current debate on issues, we investigated HTA reports and methodology of economic evaluation studies in several drugs, devices and procedures. Based on the review of these information, the research group discussed and proposed economic evaluation guideline suitable for Japan. **RESULTS:** Proposed guideline consist of 13 items: 1) Objective; 2) Perspective of analysis; 3) Comparators; 4) Method of analysis; 5) Time horizon; 6)Choice of outcomes; 7) Source of clinical data; 8) Costs; 9) Productivity loss; 10) Discounting; 11) Modeling; 12) Uncertainty; and 13) Budget impact analysis. Guideline sentences are classified into 3 levels, principal, recommended, and optional. **CONCLUSION:** This guideline is a proposal by a research team. However, it will be needed in the near future for using economic evaluation of health care technologies. Proposed guideline should be tested by adopting individual studies.

PRM219

DEALING WITH ZERO CELLS IN SPARSE NETWORKS IN BAYESIAN NETWORK META-ANALYSIS

Ivanescu C[1], Skaltsa K[2], Heemstra L[1], Van Engen A[1]
[1]Quintiles, Hoofddorp, The Netherlands, [2]Quintiles, Barcelona, Spain

OBJECTIVES: Bayesian Network Meta-Analysis (NMA) models for binary data are well established and special precautions do not usually need to be taken in the case of zero cell counts. Furthermore, trials with zero cells in both arms are usually excluded from the analysis. However, in sparse networks with only one trial per comparison and zero cells in unique link studies, their inclusion may be mandatory. Zero frequencies may result in numerical instability and/or large variances. The objective of this study was to investigate the effect of different methods dealing with zero cells in sparse networks in Bayesian NMA. **METHODS:** A review was conducted to identify methods dealing with zero cells for binary outcomes in sparse networks in a Bayesian setting. The identified methods were applied to a sparse network with six treatments and one study per comparison. The outcome was grade 3+ Adverse Events and measured by Odds Ratio. A fixed effects model was fitted with binomial likelihood. The performance of the methods was assessed by the residual deviance and the Credible Intervals' (CrI) width was compared. **RESULTS:** We identified three methods: apply a continuity correction (a constant factor of 0.5 or the reciprocal of the opposite treatment size), use of informative priors on treatment effects and placing a distribution on the baseline model. We applied all methods and combinations of them. The model fit was adequate for all methods (residual deviance [10;12.3] for 12 datapoints). The use of different informative priors improved the variability estimates. CrI widths were reduced up to 15 times with respect to the original model with vague priors. **CONCLUSIONS:** Although the debate on the inclusion of studies with zero events in NMA is still open, our research shows that methods are available to address this issue. However, no clear recommendations can be provided.

PRM220

QUALITY ASSESSMENT OF OBSERVATIONAL STUDIES FOR SYSTEMATIC REVIEWS

Kiss N, Tongbram V, Fortier KJ
Oxford Outcomes, Morristown, NJ, USA

Observational studies are frequently included in systematic reviews, especially in those disease areas where RCTs are limited. While there are very specific tools for and guidance on assessing the quality of RCTs, the assessment of observational studies is less standardized. OBJECTIVE: To understand and assess the different tools used to review the quality of observational studies and to make recommendations based on our evaluation. **METHODS:** First, a systematic review of literature from 2005-present was conducted in Embase and Medline to determine the frequency of use of quality assessment for observational studies and the type of tools used to conduct the assessment. Second, we reviewed documentation from NHS guidance on quality assessment of non-randomized studies. Finally, we reviewed two years of approved HTA submissions to see what methods of assessment have been used for submissions. **RESULTS:** A total of 1429 articles were screened. Compared to a similar study on older literature, our review found an increase in the use of quality assessment for observational studies. However, we found that many studies continue to devise their own tool or adapt existing tools rather than use a tool in its entirety. Downs and Black, MOOSE, and STROBE were the most referenced tools, although STROBE was not originally intended for such use. Guidelines centered on "non-randomized" studies were mixed and were not always found to be applicable to observational studies, but instead mostly to single-armed clinical trials. **CONCLUSIONS:** There is still a need for guidance and standardization for observational studies assessment for use in systematic literature reviews. Although quality assessment of observational studies is still not standardized, there are a few methods becoming more frequent in the literature but are difficult to compare across systematic literature reviews because they have often been adapted by each author.

PRM221

AN APPROACH FOR QUANTIFICATION OF PATIENT ADVOCACY GROUP INPUT IN THE HTA PROCESS

Hicks N[1], Toumi M[2]
[1]Commutateur, Paris, France, [2]University Claude Bernard Lyon 1, Lyon, France

Patient input in HTA pathways by the appropriate disease Patient Advocacy Group (PAG) uses principally humanistic and social studies as an evidence base followed by critical evaluation against traditional CEA (Cost Effective Analysis) via a scientific process. Patient and Public Involvement (PPI) in HTA is associated with a low evidence base potentially limiting its value. Research presented at ISPOR 2012 by the same authors concluded a need to improve and standardize PAG input integration in HTA decision making. To investigate the way different forms of knowledge / experience are used by PAGs in NICE HTA for guideline development and new technology review. We will look at: 1) Influence of PAG structure, resource capability, internal process and the impact of PAG advisory board physician representatives on scientific validation of patient input in HTA participation, and 2) Part I results will inform further research into selection and ranking criteria of social derived data compared with CEA. An iterative PPI best practice approach will be followed. Selection criteria: Five UK PAG groups (Neurological, Autoimmune, Rare disease, Cardiovascular and Oncology) will be invited to participate. The NICE PPI Unit will nominate groups when needed. Inclusion criteria: 1) willingness to participate, 2) prior involvement in guideline / new technology assessments; and 3) presence of medical advisory board. Research elements: Application of GRIPP criteria (Guidance Reporting Involvement Patient Public) to ensure a strong evidence base will guide development of an on-line survey and subsequent focus groups and interviews. The survey, designed for SAP review, will study: size of PAG, internal process for HTA involvement, previous HTA involvement, data submitted, PAG knowledge gaps and involvement of medical advisory board. Follow up by focus groups and interviews with PAG and advisory board members to identify insights/ themes.

PRM222

JUGGLING JURISDICTIONS: METHODS FOR CONDUCTING MODULAR SYSTEMATIC REVIEWS?

Thompson J, Hawkins N
Oxford Outcomes Ltd., Oxford, UK

A crucial component of a systematic review is a clear description of the disposition of studies throughout the various steps of the review process (de-duplication, abstract review, full paper review and final inclusion). This is commonly achieved using a PRISMA diagram that shows the number of inclusions and exclusions at each stage of the review. This may be supplemented with details of the reasons for exclusion. To create the PRISMA diagram it is necessary to keep an on-going count of exclusions and inclusions throughout the review process. However, this can pose a challenge where the scope of a systematic review changes from the original specification. This may happen where the set of licensed treatments or HTA requirements vary between jurisdictions or over time. In these cases, it may be time consuming to recreate the on-going counts of exclusions that correspond to the modified scope. We present a methodology for conducting a modular systematic review in which PRISMA diagrams and other descriptions of study disposition can be generated corresponding to any subsequent changes of scope. This is achieved by splitting the review into a set of 'component-reviews' defined by mutually exclusive treatment search terms that comprise the full set of possible intersections between the individual treatments. Throughout the systematic review process separate counts of abstracts, papers and studies are maintained for each of these component-reviews. The results from the component-reviews can then be combined to reflect any final review scope (based on individual treatments). We will illustrate the methodology with an example review of the comparative efficacy of licenced thiazolidinedione's (TZDs) versus placebo in patients with type 2 diabetes mellitus (T2DM) where there are two TZDs licensed in the USA (pioglitazone and rosiglitazone) but only one in Europe (pioglitazone).

PRM223

SOCIAL NETWORK ANALYSIS OF AUTHORSHIP NETWORKS AND THE IDENTIFICATION OF EXPERT ADVISORS

Stoddart SDR[1], Siddiqui MK[2]
[1]HERON Evidence Development Ltd., London, UK, [2]Heron Health Private Ltd., Chandigarh, India

OBJECTIVES: Systematic reviews are often supplemented with the use of external experts to provide guidance on the nuances of the area. This can help add context if a review is used to support trial design or health economic model development. The ideal expert would have a deep understanding of the area and be well connected to those individuals conducting trials. The aim of the current research was to assess whether social network analysis of coauthor networks could be used to rapidly and objectively identify individuals with the qualities desired in an external expert. **METHODS:** Publication lists from a recent systematic review of rheumatoid arthritis were used to produce a list of links between authors and publications. This was then imported into the Gephi program for social network analysis. Within Gephi, matrix multiplication was used to transform this network into a coauthorship network. Eigenvector centrality was then used to infer the amount of access individual authors have to the research community as a whole. The use of eigenvector centrality as a measure of influence within the author network was then validated by correlating the centrality scores of a random sample of authors against independent ratings of desirability of those individuals' expertise. **RESULTS:** The coauthor network for rheumatoid arthritis, while not completely connected, showed a high degree of connectivity (mean degree: 26, network diameter: 5). Eigenvector centrality allowed the identification of key experts, with the highest scoring experts each providing direct access to approximately half of the whole network. Eigenvector centrality measures were a reliable predictor of mean desirability scores from ten raters ($F(1,9)=20.35$, $p=0.0015$, R-squared=0.69). **CONCLUSIONS:** Social network analysis of coauthor networks provides an efficient and robust method for the identification of expertise, and can be used as part of the systematic review process.

PRM224

SYSTEMATIC REVIEW APPROACHES FOR HTA: HORSES FOR COURSES?

Kenworthy J, Langham J, Chetty M
PHMR Associates, London, UK